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SCHEDULE A

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Federal Court of Canada
Trial Division

Section de première instance de
la Cour fédérale du Canada

Date: 20000316

Docket: T-415-98

**GLAXO GROUP LIMITED and
GLAXO WELLCOME INC.**

Applicants

- and -

**THE MINISTER OF NATIONAL HEALTH AND WELFARE and
APOTEX INC.**

Respondents

REASONS FOR ORDER

O'KEEFE J.

PROCEEDINGS

[1] By originating notice of motion filed March 13, 1998, Glaxo Wellcome Inc. and Glaxo Group Ltd. ("Glaxo"), applied to this Court, pursuant to the subsection 4(1) of the *Patented Medicines (Notice of Compliance) Regulations* ("Regulations") for an Order prohibiting the Minister of Health and Welfare ("Minister") from issuing a notice of compliance to the respondent Apotex Inc. ("Apotex") in respect of its formulation of the medicine *cefuroxime axetil* and with respect of its formulation of a pharmaceutical

composition of the same, until subsequent to the expiry of Canadian Patent Nos. 1,240,313 and 1,282,331.

[2] Glaxo is the owner of Canadian Patent Nos. 1,240,313 ("'313 patent") and 1,282,331 ("'331 patent). Very generally stated, the '313 patent contains claims for the medicine cefuroxime axetil in highly pure, substantially amorphous form as well as pharmaceutical compositions of the same; and the '331 patent contains claims for a film-coated pharmaceutical composition of cefuroxime axetil wherein the film coat ruptures within 40 seconds when measured by a described test, and the tablet core disintegrates immediately following the film rupture.

[3] Attorneys for the parties appeared before me in Toronto for argument on December 16th and 17th, 1999. Upon conclusion of the arguments, I reserved judgment and advised that I would provide both a judgment and reasons for judgment at a later date. The following is my judgment and reasons.

BACKGROUND

Patented Medicines (Notice of Compliance) Regulations

[4] A brief overview of the scheme of the Regulations may be instructive at this point.

[5] The Regulations came into force on March 12, 1993. They provided that any drug manufacturer ("first person") who files a submission for a notice of compliance in respect of a drug may set out in a patent list patents containing claims for the medicine or claims for the use of the medicine, of which the first person is the owner or owner's licensee, and which the first person wishes to have included in the patent register[1].

[6] The Regulations provide as well that another manufacturer ("second person"), upon filing a submission for a notice of compliance in respect of a drug, may compare its drug with, or make reference to, a first person's drug for which a notice of compliance has been issued and in respect of which a patent list has been submitted[2]. If the second person does so, the Regulations require the second person to state, with respect to each patent listed on the register against the first person's drug, that the second person accepts that the notice of compliance in respect of its drug will not issue until the expiry of the referenced patents or make one of several allegations[3].

[7] One possible allegation provided for in the Regulations, and the relevant allegation in this case is that "no claim for the medicine itself and no claim for the use of the medicine" would be infringed by the second person making, constructing, using or

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[1]section 4

[2]subsection 5(1)

[3]*Ibid*

selling the drug for which the submission for the notice of compliance is filed[4]. The second person must provide a detailed legal and factual basis for the allegation[5]. A notice of the allegation must then be served on the first person[6].

[8] Pursuant to subsection 6(1) of the Regulations, the first person may, within 45 days of service upon it of the second person's notice of allegation, bring a motion for an order prohibiting the Minister from issuing a notice of compliance to the second person on the grounds that none of the allegations of the second person is justified. A 24 month stay of issuance of a notice of compliance is effective upon such a proceeding being launched[7].

Amended Regulations

[9] Amendments to the Regulations came into force on March 12, 1998[8]. The amendments were aimed, in part, at clarifying what had been the subject of a considerable number of litigative sorties in the past with respect to the timing of a filing of a submission for a notice of compliance by a second person. The amended

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[4]subparagraph 5(1)(b)(iv)

[5]subparagraph 5(3)(a)

[6]subparagraph 5(2)(c)(i)

[7]subparagraph 7(1)(e)

[8]SOR/98-166

Regulations state that when the second person's allegation made under subparagraph 5(1)(b) is an allegation that no claim for the medicine itself or use of the medicine, contained in the first person's patent, would be infringed by the second person, the filing of a submission for a notice of compliance must precede or be affected contemporaneously with the making of the allegation.

[10] Subsection 5(3) of the 1993 Regulations stated as follows:

5.(3) Where a person makes an allegation pursuant to paragraph (1)(b) or subsection (2) the person shall	5.(3) Lorsqu'une personne fait une allégation visée à l'alinéa (1)b) ou au paragraphe (2), elle doit:
(a) provide a detailed statement of the legal and factual basis for the allegation; and	a) fournir un énoncé détaillé du droit et des faits sur lesquels elle se fonde;
(b) serve a notice of the allegation on the first person and proof of such service on the Minister.	b) signifier un avis d'allégation à la première personne et une preuve de cette signification au ministre.

[11] The 1998 amendments replaced this section with the following:

Where a person makes an allegation pursuant to paragraph (1)(b) or subsection (2) the person shall	Lorsqu'une personne fait une allégation visée à l'alinéa (1)b) ou au paragraphe (2), elle doit :
(b) if the allegation is made under any of subparagraphs (1)(b)(i) to (iii), serve a notice of the allegation on the first person;	b) si l'allégation est faite aux termes de l'un des sous-alinéas (1)b)(i) à (iii), signifier un avis de l'allégation à la première personne;
(c) if the allegation is made under subparagraph (1)(b)(iv),	c) si l'allégation est faite aux termes du sous-alinéa (1)b)(iv) :
(i) serve on the first person a notice of the allegation relating to the submission filed under subsection (1) at the time that the person files the submission or at any time thereafter, and	(i) signifier à la première personne un avis de l'allégation relative à la demande déposée selon le paragraphe (1), au moment où elle dépose la demande ou par la suite,

...

...	
(d) serve proof of service of the information referred to in paragraph (b) or (c) on the Minister.	d) signifier au ministre une preuve de la signification effectuée conformément aux alinéas b) ou c).

[12] The regulatory impact statement, although not forming a part of the Regulations, is abundantly clear and provides the rationale for the amendments:

> No Premature NOA: An NOA relating to non-infringement may only be served on a patentee by a generic manufacturer when or after it has filed a submission for an NOC with the Minister of Health.

[13] Also contained in the amendments to the Regulations were various transitional provisions, one of which held that the amendments to subsection 5(3) would not apply to an allegation:

9. (1) ... if, before the coming into force of these Regulations, it was served on the first person, if proof of that service was served on the Minister and if the first person has commenced a proceeding under subsection 6(1).	9. (1) ... si, avant l'entrée en vigueur du présent règlement, elles ont été signifiées à la première personne, si la preuve de leur signification a été signifiée au ministre et si la première personne a présenté une demande aux termes du paragraphe 6(1).

The Apotex Allegation

[14] Pursuant to the procedures outlined in the Regulations, Glaxo has previously submitted patent lists to the Minister for inclusion in the patent register maintained under the Regulations. The '313 and '331 patents were among the patents included in Glaxo's submissions.

[15] On January 22, 1998, Apotex forwarded to Glaxo a letter which purported to be a notice of allegation. With respect to the '313 patent, Apotex alleged that no claim of the patent would be infringed by its "making, constructing, using or selling...tablets containing cefuroxime axetil." In particular, Apotex alleged that any tablets made and sold by it would "be made using pure cefuroxime axetil only in crystalline form." And with respect to the '331 patent, Apotex alleged that any tablets made and sold by it would not disintegrate immediately after rupture of the outer film coating, but would have a disintegration time of at least several minutes after rupture of the film.

[16] I will now turn to a consideration of the circumstances of the case at bar. I begin with the preliminary procedural issues raised by the parties and will then deal with the substantive issue of whether the Apotex allegation is not justified.

PRELIMINARY ISSUES

Compliance with the Regulations

[17] In its submissions before me, Glaxo raised two preliminary issues. Glaxo argued that Apotex had not complied with the Regulations by:

(a) not setting out a sufficiently detailed legal and factual basis for its allegation;

(b) not filing a submission for a notice of compliance prior to serving its notice of allegation on Glaxo.

a) Transitional Provisions

[18] There was some debate before me with respect to the interpretation to be given the transitional provisions contained in subsection 9(1) of the recent amendments to the Regulations. Apotex claimed that the provision required only that the notice of allegation be served prior to the coming into force of the amended Regulations to avoid the operation of the amendments, while Glaxo claimed that all three listed events must have occurred in order to avoid their application. The issue is only relevant at all insofar as there is a question as to whether Apotex has complied with the provisions of the new section 5 and had filed a submission for a notice of compliance prior to issuing its notice of allegation to Glaxo. It is clear that the Apotex allegation is an allegation of non-infringement (subparagraph 5(1)(b)(iv)) such that the amendments, if they are held to apply to this case, will be operative to require that a submission for a notice of compliance precede service of a notice of allegation.

[19] Glaxo has raised the issue that the new drug submission (NDS) must be filed at or before the time of serving a notice of allegation on a first person (paragraph 12 of the notice of motion) but no evidence has been led to show whether or not the NDS was filed. Glaxo raised this issue and since no evidence was led, I cannot rule that this

argument has any merit. Simply put, I do not know that a NDS was not filed before the service of the allegation..

[20] Subsection 6(1) provides for the right of action of the first person:

6.(1) A first person may, within 45 days after being served with a notice of an allegation pursuant to paragraph 5(3)(b) or (c), apply to a court for an order prohibiting the Minister from issuing a notice of compliance until after the expiration of a patent that is the subject of the allegation.	6.(1) La première personne peut, dans les 45 jours après avoir reçu signification d'un avis d'allégation aux termes des alinéas 5(3)b) ou c), demander au tribunal de rendre une ordonnance interdisant au ministre de délivrer un avis de conformité avant l'expiration du brevet visé par l'allégation.

[21] And subsection 6(2) provides for the jurisdiction of the Court:

6.(2) The court shall make an order pursuant to subsection (1) in respect of a patent that is the subject of one or more allegations if it finds that none of those allegations is justified.	6.(2) Le tribunal rend une ordonnance en vertu du paragraphe (1) à l'égard du brevet visé par une ou plusieurs allégations si elle conclut qu'aucune des allégations n'est fondée.

[22] Glaxo argued that the Minister does not have jurisdiction to issue a notice of compliance until subsequent to the filing of the new drug submission, and effectively, that a notice of allegation that precedes a submission for a notice of compliance is a nullity. While this may be correct, I am unable to make a decision on this ground for the reasons given in paragraph 19. Glaxo has asked this Court to issue an order of prohibition, pursuant to the Regulations, and the basis for the Court doing so is a finding that none of the allegations of the second person (Apotex) are justified.

[23] It is true however that Section 7 provides that the *Minister* is prohibited from issuing a notice of compliance until "the day on which the second person complies with section 5.":

7.(1) The Minister shall not issue a notice of compliance to a second person before the latest of	7.(1) Le ministre ne peut délivrer un avis de conformité à la seconde personne avant la plus tardive des dates suivantes :
(b) the day on which the second person complies with section 5	b) la date à laquelle la seconde personne se conforme à l'article 5

[24] If Apotex has not complied with section 5, it will have to face the consequences.

[25] There is some question as to whether the case before the Court is moot, or premature in the event that no submission for a notice of compliance has been made by Apotex and the Minister will be presumed to refuse to issue a notice of compliance until section 5 is complied with. I leave the question open, as Glaxo has not argued that this is the case in this motion and has not, at least until very recently, attempted to make use of the disclosure provisions of subsection 6(7) of the Regulations; which would have enabled Glaxo to inform itself as to whether there was in fact such a submission filed with the Minister.

Adequacy of the Apotex Allegation

[26] Glaxo has also argued that it is not possible to conclude that the Apotex

formulation would fall outside the scope of the claims of the '313 and '331 patents based on the factual and legal basis provided in the Apotex notice of allegation.

[27] The Regulations provide that the second person must state the legal and factual basis for its allegation in its notice of allegation to the first person. Glaxo complains that the Apotex allegation is deficient, in that it does not provide a sufficient legal and factual basis for the allegation and, in fact, that the facts as stated do not support a finding of non-infringement.

[28] As mentioned earlier, the Apotex allegation stated with respect to the '313 patent, that its starting material would be pure crystalline cefuroxime axetil, rather than amorphous. And with respect to the '331 patent, Apotex states that any tablet formulations used by Apotex would not disintegrate immediately after the film rupture, but would take several minutes to disintegrate.

[29] The required scope of the legal and factual basis for the allegation was considered by the Appeal Division of this Court in *Bayer AG* v. *Canada* (1996) 51 C.P.R. (3d) 329. The Court found that a bald assertion of non-infringement was insufficient, but that it was permissible for the second person to withhold certain information regarding its formulation until subsequent to a confidentiality order being issued. This apparently was settled as a standard procedure to be followed in cases such as the case at bar.

[30] In light of this decision, it is my view that Glaxo's preliminary objection to the

adequacy of the factual basis of the Apotex allegation is without merit. While the mere fact that the starting material in the Apotex formulation is cefuroxime axetil in crystalline form may, depending upon the construction of the '313 patent that I adopt, be an insufficient basis for concluding that the '313 patent would not be infringed, it does not follow from this that the Apotex allegation is not justified. The Apotex further disclosure elaborated on the basis for which the allegation of non-infringement was made such that there is sufficient evidence upon which to evaluate the allegation. This procedure was approved by the Appeal Division in *Bayer AG, supra.*

[31] In determining whether the allegation itself is unjustified, it is necessary to litigate the issues–as was certainly done in the case at bar. Glaxo has quoted the following passage from *Merck Frosst Canada Inc.* v. *Canada (Minister of Health & Welfare)* (1994), 55 C.P.R. (3d) 302 (F.C.A.):

> "In determining whether or not the allegations are "justified", the Court must then decide whether, on the basis of such facts as have been assumed or proven, the allegations would give rise in law to the conclusion that the patent would not be infringed by the Respondent."

[32] Although apparently relied upon as support for Glaxo's position, the passage merely confirms that, after having heard the motion, the question facing the Court is whether, on the basis of the facts proved in the proceeding, the allegation–in this case, the allegation of non-infringement–is not justified.

[33] I now move on to the substantive issues of whether the Apotex allegation is not

justified. I do this by constructing the individual patents and then analysing the evidence of the Apotex process.

JUSTIFICATION OF THE APOTEX ALLEGATION

Burden of Proof

[34] As a preliminary issue to the consideration of the issues in the case at bar, I note that a legal burden rests on the applicant, Glaxo, to demonstrate to the Court, on a balance of probabilities, that the Apotex allegation is not justified. This is the standard adopted by the Appeal Division in *Hoffman-La Roche* v. *Canada* (1996), 70 C.P.R. (3d) 206.

Principles of Patent Construction

[35] In order to determine whether the Apotex allegations are not justified, the '313 and '331 patents must be constructed and the scope of the monopoly claimed by the patents determined. To this end, reference will be made to well-established principles of patent construction. These principles of patent construction apply in this case even though this is not a patent infringement action per se–for if I determine from the construction of the patent that the making or marketing of the Apotex formulation, as described in the evidence before me, would infringe Glaxo's '313 and '331 patents, the Apotex allegations of non-infringement would necessarily not be justified.

[36] The principles of patent construction are well settled and without apparent controversy. According to leading textbook writers[9], the patent should be constructed in a purposive way, in order to give effect to the purpose of the invention, without the Court being either benevolent nor unduly harsh. The claims are to be read from the perspective of a person skilled in the art in question, with a mind willing to understand.

[37] More specifically stated, the following canons of construction must be followed[10]:

(a) The claims are to be construed with reference to the entire specification.

(b) The claims are to be construed without reference to the prior art.

(c) Each claim is, if possible, to be given a distinct meaning.

(d) What is not claimed is disclaimed.

[38] Finally and importantly, the patent is to be constructed *before* determining the question of infringement of the patent and separate from any determination in that regard.

The '313 Patent

[39] I will now construe the '313 patent on the basis of the principles outlined above.

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[9]H.G. Fox., *Canadian Patent Law and Practice* (4th ed). (Toronto: Carswell, 1969)

[10]*Ibid*

It will be necessary mainly to consider the question from the perspective of construction of the two claims that are really in issue in this case: claim 15 and claim 18.

[40] The '313 patent contains claims for the medicine cefuroxime axetil in highly pure, substantially amorphous form. The disclosure to the '313 patent states as follows:

> "In view of past experience in the cephalosporin field, we first prepared cefuroxime axetil for commercial evaluation in substantially pure, crystalline form. We have however surprisingly found that substantially pure, crystalline cefuroxime axetil does not have the best balance of properties for commercial use and that, contrary to previous experience in the cephalosporin field, cefuroxime axetil is advantageously used in a highly pure, substantially amorphous form. We have thus established that highly pure, cefuroxime axetil when in substantially amorphous form has higher bioavailability upon oral administration that when in crystalline form and that moreover the amorphous form of cefuroxime axetil has adequate chemical stability upon storage.
>
> The cefuroxime axetil in accordance with the invention preferably contains less than 5% mass/mass (m/m), advantageously less than 3% m/m, of impurities. It is to be understood that references herein to 'impurities' are to be understood as not including residual solvents remaining from the process used in the preparation of the cefuroxime axetil of the invention. Any residual solvent present will desirably only be present in less than 6% m/m and most preferably less than 2% m/m.
>
> ...
>
> Suitable solvents for dissolving cefuroxime axetil to form solutions from which recovery is enabled include organic solvents, for example ketones, e.g. acetone and mixtures thereof, if desired with other solvents, e.g. water
>
> In general, we have found that the cefuroxime axetil has sufficient heat stability to withstand spray drying and accordingly spray drying is a preferred method of effecting recovery. Spray drying systems can be operated in a known manner to obtain an amorphous product essentially free from crystalline material and free from particulate contaminants.
>
> The preparation of a composition suitable for forming into tablets, capsules or granules may also be achieved by spray-drying or roller drying a suspension of pure amorphous cefuroxime axetil with the excipients appropriate for the said tablets, capsules or granules."

[41] To summarize my understanding of this disclosure, a starting material of cefuroxime axetil, most likely in crystalline form is, using well known methods in the art, dissolved in a solution of water and acetone. These solvents are evaporated through spray drying or other methods, and what remains is cefuroxime axetil in an amorphous

form, being distinguished from crystalline. The matter remaining after the spray drying of the solvents having a random dispersion of molecules, includes a small amount of residual solvent-water and acetone-but in small quantities. In addition, impurities resulting from the formation of the cefuroxime axetil itself are present, in small quantities, with the disclosure listing certain typical impurities that may be expected to be present.

[42] The disclosure to the patent also explicitly states that the reference to "impurities" does not include the residue from the solvents. The focus for the purity analysis is on the cefuroxime axetil itself. The particular issues at play in the construction of the '313 patent are the level of purity required to come within the claims of the patent and the determination of what constitutes an impurity.

[43] The contentious issues in this case revolve around the interpretation and construction of two claims of the '313 patent:

> "15. Cefuroxime axetil in highly pure, substantially amorphous form.
>
> 18. A pharmaceutical composition comprising cefuroxime axetil in highly pure, substantially amorphous form, in admixture with one or more pharmaceutical carriers or excipients."

[44] The evidence adduced before me indicates that cefuroxime axetil is found in either crystalline or amorphous form. As I understood it, the terms are mutually exclusive. Crystalline forms of matter have a predictable structure and long range order. Materials with an amorphous form have no such long range order. Therefore, in light of

the language of the claim, and the knowledge of those skilled in the art, crystalline cefuroxime axetil, pure or otherwise is not claimed by the '313 patent.

[45] I do not believe that the meaning of the word "substantially" as a modifier to the adjective "amorphous" has been at issue in these proceedings. There is little evidence before me as to what a person skilled in the art would consider "substantially" to mean. The Apotex affiant, Dr. Sherman, stated in cross-examination that in his mind, "substantially amorphous" meant that the matter was essentially free from crystalline material. Suffice it to say that I believe that the general, overriding characteristic of the cefuroxime axetil in question must hold the characteristic of being amorphous, lacking specific long range order, in order to be within the claims of the '313 patent.

[46] With respect to the required purity, the patent claims "highly pure" cefuroxime axetil. For the purposes of this judgment, pure cefuroxime axetil will be characterized as being composed of 100 percent cefuroxime axetil. The claims do not require that the cefuroxime axetil be completely pure–it need only be "highly pure".

[47] The disclosure to the patent states that typical impurities contained in the sample will be residue from the formation of cefuroxime axetil and will preferably represent less than 5 percent of the weight of the entire sample. The disclosure also specifically excludes solvent residue remaining from the formation of the amorphous cefuroxime axetil as being considered as an impurity.

[48] The evidence before me with respect to the question of the level of purity claimed by the reference in the '313 patent to "highly pure cefurxoime axetil..." was varied. Dr. Sherman, affiant for Apotex, claimed that a purity of at least 95 percent and perhaps as high as 98 or 99 percent would be required in order for a person skilled in the art to state that a particular product was "highly pure". While Dr. Winterborn, Glaxo affiant, stated that a person skilled in the art would not consider a substance deliberately added to a formulation to be an impurity.

[49] Making reference to the specification and disclosure to the '313 patent, I note that the level of impurity is "preferably" less than 5 percent and "advantageously" less than 2 percent, when expressed as a percentage of the weight of the entire substance that is represented by the impurity. And while the claims outline the scope of the monopoly claimed by the patentee, the specification can be useful as an interpretive tool and can guide the Court in consideration of what a person skilled in the art would consider "highly pure" to mean. These persons skilled in the art are, ultimately, the audience to which the disclosure to the patent is directed. The portion of the disclosure which makes reference to impurities states as follows:

> "The cefuroxime axetil in accordance with the invention preferably contains less than 5% mass/mass, advantageously less than 3% mass/mass of impurities. It is to be understood that references herein to 'impurities' are to be understood as not including residual solvents remaining from the process used in the preparation of the cefuroxime axetil of the invention."

[50] Given the disclosure to the invention, it is preferred that less than 5 percent

impurities be present. It is most advantageous that less than 2 percent impurities are present. Therefore, a purity of between 100 percent and 95 percent may be the limit of the claims of the patent. But I do not consider such to follow absolutely. Nonetheless, it must be borne in mind that the invention is presumably useful and that such usefulness must be derived from the characteristics described in the claims and disclosure to the patent. Also, the evidence of Dr. Sherman was that individuals skilled in the art would consider impurities representing 10 percent of the mass of the substance as being a "pure" substance. While I am considering "pure" to mean 100 percent purity, Dr. Sherman apparently considers a "pure" substance to have greater impurities than a "highly pure" substance. This is basically a matter of semantics.

[51] For his part, Dr. Winterborn based his evidence with respect to purity levels solely on the contention that substances deliberately added to cefuroxime axetil would not be considered to be an impurity by those skilled in the art.

[52] In light of the evidence before me, I conclude that purity levels of between 95 percent and 100 percent are within the claims of the '313 patent. Therefore, in order to infringe claim 15 of the patent, the cefuroxime axetil in question must be principally in amorphous form with a purity of between 95 percent and 100 percent.

[53] I now turn to claim 18:

> "18. A pharmaceutical composition comprising cefuroxime axetil in highly pure, substantially amorphous form, in admixture with one or more pharmaceutical carriers or excipients."

[54] This claim merely extends the monopoly from the actual physical product of amorphous cefuroxime axetil to pharmaceutical formulations (tablets) in admixture with pharmaceutical carriers or excipients. These excipients are widely used and well known to persons skilled in the art. They provide a method of delivery of medicines, in this case the active ingredient being cefuroxime axetil.

[55] Keeping in mind that one of the canons of construction is that "what is not claimed is disclaimed" and also in consideration of the disclosure to the patent, which explains how persons skilled in the art act upon the active ingredient in order to produce such pharmaceutical formulations, the scope of this claim appears to me to be rather limited and appears not to add much to claim 15. Claim 18 merely extends the monopoly with respect to the highly pure, substantially amorphous cefuroxime axetil formulation, to include this substance in a pharmaceutical composition.

[56] The wording of the claim is that the cefuroxime axetil be in admixture with one or more pharmaceutical carriers or excipients. Admixture has been defined as a physical mixing together. Indeed, the disclosure to the patent describes processes for the physical mixing of various additives or non-active or essential substances in order to produce a pharmaceutical tablet. The language of claim 18 is however in my view broad enough to cover any similar admixture.

Apotex Formulation

[57] I will now consider the evidence with respect to the nature of the Apotex formulation in order to determine whether such would infringe Glaxo's '313 patent.

[58] The Apotex formulation was described in its further disclosures provided subsequent to the issuance of a confidentiality order in this action. In brief, the Apotex formulation proceeds as follows:

> "...as the first step in our production of tablets, the crystalline cefuroxime axetil is dissolved along with sorbitol in an acetone/water mixture and dried to from a co-precipitate. Since the cefuroxime axetil is dissolved in the process, there would, in any event, obviously be no benefit from using amorphous cefuroxime axetil instead of crystalline in such a process."

[59] Apotex uses 9 parts cefuroxime axetil for 1 part sorbitol to create its coprecipitate. From this point, magnesium stearate and colloidal silicone dioxide are added to the coprecipitate and mixed. The mixture is compacted and then ground into granules. The granules are then mixed with croxpovidone, granular sodium bicarbonate, additional magnesium stearate and colloidal silicone dioxide and compressed into tablet cores of 500 mg, 250 mg, and 125 mg strengths before being film coated.

[60] It has been admitted by Apotex that there is no chemical reaction, such that a

different or new chemical substance can be said to have been created upon the formation of the coprecipitate. Dr. Sherman stated that a "new substance" was created. This is a confusing choice of words. It was however apparently true, since the coprecipitate is clearly a "new substance" when compared to what was present at the beginning of the process, crystalline cefuroxime axetil.

[61] As Dr. Sherman explains it, there is a homogenous dispersal of the cefuroxime axetil and sorbitol at the molecular level. Throughout the substance that remains from the process, these molecules are arranged in an amorphous form. There is no chemical reaction. The mixture represents a "dispersion at the molecular level." If one were to pick out one molecule of the coprecipitate, its smallest component part, one would find that it consisted of, by molecular weight, 90 percent cefuroxime axetil and 10 percent sorbitol, with possible very slight variations. There would be no molecules composed entirely of cefuroxime axetil.

[62] For its part, Glaxo through its evidence states that the fact that the product is a coprecipitate and not a physical admixture does not prevent the Apotex formulation from infringing the claims of the '313 patent. According to Dr. Winterborn, since there is no chemical reaction, there is no change in the substances, and cefuroxime axetil continues to exist in the end product.

[63] In addition, Dr. Winterborn attests that dissolution of cefuroxime axetil in an

acetone and water solution followed by spray drying will yield substantially amorphous cefuroxime axetil. Furthermore, Dr. Winterborn tendered the opinion that the coprecipitate is amorphous, and also his belief that an admixture of amorphous cefuroxime axetil and amorphous sorbitol would be indistinguishable, on X-ray powder analysis, from the Apotex coprecipitate.

[64] On a review of the evidence, it is clear that Apotex does not allege that the coprecipitate is not amorphous. Apotex expressly declines to state what the nature of the coprecipitate is, as it is of the view that such a consideration is irrelevant to the question of whether claim 18 is infringed. According to Apotex, even if it is stated that the coprecipitate is amorphous, given the presence of sorbitol it is not possible to state that the cefuroxime axetil present in the coprecipitate is amorphous.

[65] Apotex for its part, points to the creation of the cefuroxime axetil and sorbitol coprecipitate as being a mass which cannot be said to be cefuroxime axetil at all. But this does not mean that there is not cefuroxime axetil in substantially amorphous form. Indeed, if I am of the view that if the cefurxoime axetil in this formulation is substantially amorphous, and also highly pure, the '313 patent will be infringed and the Apotex allegation will be unjustified. The fact that sorbitol is mixed in with the cefuroxime axetil may make such a determination more difficult, but such does not avoid infringement.

[66] I must say that I am not convinced that the process undergone by the cefuroxime axetil in the procedure described by Apotex is as significant Apotex states. Without a chemical reaction, there would apparently still be cefuroxime axetil in the coprecipitate, but it would be interdispersed along with the sorbitol. As I mentioned in the patent construction stage, such an unnecessary intermediate step undertaken prior to formation into a tablet would not avoid infringement of the patent per se. Whatever the effect of the creation of the co-precipitate, if there is highly pure substantially amorphous cefuroxime axetil within it, the '313 patent is infringed.

[67] While the evidence before me is clear that the coprecipitate is amorphous, there was in my view insufficient evidence for me to find that the cefuroxime axetil is amorphous. By the methods described, it is difficult to separate out the components and determine if such is the case. I am therefore not persuaded on a balance of probabilities that the Apotex coprecipitate contains substantially amorphous cefuroxime axetil.

[68] This was a difficult determination, and one that only rested on the burden of proof in this case. Since the burden is Glaxo's, there can be no ruling that the Apotex allegation is not justified when I am in a state of uncertainty as to the exact nature of the coprecipitate. I am unable to find that there is in fact, substantially amorphous cefuroxime axetil in the Apotex coprecipitate.

[69] But there is a second aspect of the claim to the patent: the cefuroxime axetil must

also be highly pure. And as discussed above, this means that the purity must be in excess of 95 percent. The evidence adduced by Dr. Sherman indicated that the impurities present in the substance subsequent to the creation of the coprecipitate were in excess of 20 percent. This is accounted for by the 10 percent sorbitol addition, and "up to" 10.4 percent of other materials. It was unclear to me whether solvent residue was included in this 10.4 percent–as these "impurities" were specifically excluded from the definition. However, as Dr. Sherman admitted in cross-examination that even water had been included as an impurity, which was not proper, I am satisfied that solvent residue was also included as an impurity when arriving at these figures.

[70] But, notwithstanding this uncertainty, the presence of 10 percent sorbitol in and of itself is sufficient to take the Apotex coprecipitate out of the league of "highly pure" cefuroxime axetil. This will, however, only be the case if the sorbitol can be properly characterized as an impurity.

[71] I am mindful of the evidence of Dr. Winterborn, who stated that a person skilled in the art would not consider a substance deliberately added to another substance to be an impurity. I would have accepted this in different circumstances. But in the circumstances of this case, the situation is different from that contemplated by Dr. Winterborn. For instance, certainly the pharmaceutical excipients and additives physically admixed with cefuroxime axetil referred to in the claim 18 would not be considered impurities. But here we have a starting material of crystalline cefuroxime

axetil which is put through a process: it is dissolved along with sorbitol in an acetone and water solution, with the solute then evaporated off, leaving a "coprecipitate," comprised of the cefuroxime axetil and sorbitol. And these substances are dispersed at the molecular level. One molecule of the coprecipitate is 90 percent cefuroxime axetil and 10 percent sorbitol by molecular weight. This is a different situation from the physical admixture described in Glaxo's patent.

[72] I also note the evidence of Dr. Shefter, who stated that the sorbitol is properly characterised as an "ordinary impurity" pursuant to the definition in the United States Pharmacopeia. This definition is produced at page 500 of the Applicant's Motion Record:

> "Ordinary impurities are those species in bulk pharmaceutical chemicals that are innocuous by virtue of having no significant, undesirable biological activity in the amounts present. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles."

[73] Having been put through the described process, I believe that the sorbitol is to be considered an impurity, resulting from the preparation of the coprecipitate.

[74] As a result of this finding the coprecipitate simply cannot be said to be highly pure cefuroxime axetil. I have previously found that I am not satisfied on a balance of probabilities that any cefuroxime axetil present is in amorphous form. But with the process undertaken by Apotex, I find that there is not highly pure cefuroxime axetil present.

[75] Apotex argues that since the claims of the '313 patent claim highly pure cefuroxime axetil in substantially amorphous form, the proper construction of the patent is that both of these must be present in the same substance. I agree. If the cefuroxime axetil is not highly pure and/or if it is not substantially amorphous there would be no infringement and the Apotex allegation would be justified. I have found such to be the case with respect to the '313 patent.

The '331 Patent

[76] The disclosure to the '331 patent provides for a tablet which aims to provide a greater level of absorbtion and effectiveness of the medicine cefuroxime axetil than previous formulations. The disclosure indicates that in the prior art, the tablet core could form a gelatinous mass and reduce the disintegration and thus level of absorption and effectiveness of the medicine. This occurred with both crystalline and amorphous cefuroxime axetil. Glaxo found that the problem of gelling could be overcome by preparing a film coated tablet which ruptures rapidly upon contact with the stomach and intestinal fluid and the core immediately disintegrates. The tablet core can be made to disintegrate quickly using methods well known in the art, notably by the use of disintegrants.

[77] Claim 1 of the patent states:

> "1. A pharmaceutical tablet for oral administration which comprises a tablet core containing an effective amount of cefuroxime axetil as active ingredient and a film coat which serves to mask the bitter taste of cefuroxime axetil upon oral

> administration, the film coat having a rupture time of less than 40 seconds when measured by a rupture test wherein the tablet is placed in a beaker of still 0.07 M hydrochloric acid at 37 C , the rupture time being measured as the time which elapses before the core of the tablet first becomes visible to the naked eye through the ruptured film coat and the tablet core disintegrating immediately following rupture of the film coat in the said rupture test."

[78] In constructing this patent, I find that the scope of the protection afforded by the '331 patent, and all the claims thereto, clearly provides that the monopoly claimed is on those formulations and film coats which produce a rupture of less than 40 seconds. That is plain and obvious based on the clear language of the claim. But what was at issue in the case at bar was the scope of the monopoly claimed with respect to the speed of disintegration of the tablet core, subsequent to outer coat rupture.

[79] The patent itself merely states that the tablet core "disintegrat[es] immediately following rupture of the film coat in the said rupture test". The word "immediately" is not defined, nor is there much guidance in the disclosure as to what is meant by it. There are illustrations of disintegration which indicate that it is effected in approximately 10 seconds. I believe that it suffices it to say that disintegration would be very rapid.

[80] The only evidence before me as to what persons skilled in the art would consider to be immediate disintegration was that provided by Dr. Sherman, who stated that disintegration time of up to one minute would be considered as immediate disintegration. There was also evidence that certain pharmaceutical tablets have disintegration times of over one hour. Given this, I believe the '331 patent should be considered to claim

disintegration times of up to one minute. Were it not for the evidence of Dr. Sherman, I would have come to the conclusion that a much shorter disintegration time was claimed.

[81] Much of Glaxo's submissions with respect to the '331 patent were related to the experimentation conducted by Dr. Sherman on the Apotex formulation, where it was found that disintegration took "many minutes". Dr. Sherman attested that the tablet disintegrated with effervescence and the tablet continued to shed mass over many minutes. The disintegration stopped "without being complete." It was later stated that the tablet had a palpably firm core at the time that the disintegration with effervescence stopped.

[82] Glaxo submitted that the evidence of Dr. Sherman was suspect and that in any event, given the definition of "disintegrate" given in the United States Pharmacopeia he clearly misapprehended what he was observing and his evidence was therefore of little value.

[83] I was unimpressed by these submissions. Regardless of what definition is used, the tablet core, according to Dr. Sherman continued to effervesce for several minutes and stopped, at which time, the tablet still had a palpably firm core. And this is to be distinguished against the Glaxo '331 patent, wherein the tablet core disintegrates "immediately", defined here as within one minute.

[84] I will not accede to Glaxo's urgings and reject Dr. Sherman's evidence in its

entirety. There is simply no basis upon which I could do so. Glaxo was unable to impeach Dr. Sherman in cross examination and relied upon the argument that the definition of "disintegrate" rendered the observations of Dr. Sherman of little utility. The evidence of Dr. Winterborn, which stated his opinion that the tablet would disintegrate immediately is also of no help to Glaxo, it is merely a belief, balanced against the express statements from Dr. Sherman which state the opposite. This conflict in the evidence will not be resolved in favour of Glaxo.

[85] The evidence adduced by Apotex representative Dr. Sherman was that he conducted the rupture test according to the Apotex disclosure, and observed the disintegration of the tablet core. He remarked that the tablet continued to shed mass for many minutes. Dr. Sherman subsequently stated that he had poked at the tablet core and discovered a firm core, thus finding that disintegration was not complete.

[86] The submissions regarding the purported misapprehension of Dr. Sherman with respect to the proper test for disintegration, as well as the submissions of Apotex with respect to the definition in the United States Pharmacopeia being non-applicable since Glaxo uses a different rupture test were the most extraneous submissions of this entire case. On its plain meaning, the testimony indicated that the Apotex formulation fell outside the claims of the '331 patent. There is simply no basis for me to reject the testimony despite the urgings of Glaxo's counsel. The evidence offered to rebut this was merely speculative. This is insufficient.

[87] Therefore, I cannot find that the Apotex allegation with respect to the '331 patent is not justified.

[88] In order to succeed in its application, Glaxo was required to prove on a balance of probabilities that the Apotex allegation, the allegation that no claim for the '313 or '331 patents would be infringed by Apotex, was unjustified. This it has failed to do.

CONCLUSION

[89] As a result of the foregoing, the application is dismissed with costs. No order of prohibition shall issue.

"John A. O'Keefe"
J.F.C.C.

Halifax, Nova Scotia
March 16, 2000

I HEREBY CERTIFY that the above document is a True copy of the original filed of record in the Registry of the Federal Court of Canada the 16 day of March A.D. 2000

Dated this 16 day of Mar 2000

FRANCOIS PILON

FEDERAL COURT OF CANADA
Names of Counsel and Solicitors of Record

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